Clinical Infectious Diseases Advance Access published February 27, 2014

Outbreak of Measles Among Persons With Prior Evidence of Immunity, New York City, 2011

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Summary (40 words): A measles outbreak occurred in New York City. All cases had prior evidence of measles immunity. Symptoms were consistent with measles. Laboratory results indicated secondary immune responses. This is the first report of measles transmission from a twice vaccinated individual.

Abstract

Background. Measles was eliminated in the United States through high vaccination coverage and a public health system able to rapidly respond to measles. Measles may occur among vaccinated individuals, but secondary transmission from such individuals has not been documented.

Methods. Suspected cases and contacts exposed during a measles outbreak in New York City in 2011 were investigated. Medical histories and immunization records were obtained. Cases were confirmed by detection of measles-specific IgM and/or RNA. Tests for measles IgG, IgG avidity, measurement of measles neutralizing antibody titers, and genotyping were performed to characterize the cases.

Results. The index case had two doses of measles-containing vaccine. Of 88 contacts, four secondary cases were confirmed that had either two doses of measles-containing vaccine or a past positive measles IgG antibody. All cases had laboratory confirmation of measles infection, clinical symptoms consistent with measles, and high avidity IgG antibody characteristic of a secondary immune response. Neutralizing antibody titers of secondary cases reached >80,000 mIU/mL 3-4 days post-rash onset while that of the index was <500 mIU/mL 9 days post-rash onset. No additional cases occurred among 231 contacts of secondary cases.

Conclusions. This is the first report of measles transmission from a twice vaccinated individual. The clinical presentation and laboratory data of the index were typical of measles in a naïve individual. Secondary cases had robust anamnestic antibody responses. No tertiary cases occurred despite numerous contacts. This outbreak underscores the need for thorough epidemiologic and laboratory investigation of suspected measles cases regardless of vaccination status.

Background

Before the introduction of measles vaccine, over 90% of the United States (U.S.) population contracted measles by age 15 years[1]. Following the introduction of measles vaccine in 1963, measles incidence declined rapidly[2]. In 1989, the Advisory Committee on Immunization Practices (ACIP) recommended a second dose of measles vaccine, as combined measles-mumps-rubella (MMR) vaccine, for introduction into the routine immunization schedule[3]. Adherence to this recommendation combined with sustained, high national MMR vaccination coverage helped eliminate endemic measles transmission by 2000 [4, 5]. Measles remains endemic in many parts of the world, and international travelers with measles may transmit virus to non-immune individuals in the U.S[2]. In 2011, the U.S. recorded 222 measles cases, of which 86% were unvaccinated or had undocumented vaccination status, indicating that failure to vaccinate is the most significant cause of measles following importation[6]. The ongoing risk of importations requires sustaining high levels of population immunity to maintain measles elimination in the U.S.

The ACIP criteria for presumptive evidence of immunity to measles include documented receipt of two doses of live measles virus–containing vaccine, laboratory evidence of immunity, or birth before 1957[6, 7]. Although vaccination with two doses of MMR vaccine is highly effective and is a proxy for immunity to measles, cases of measles have occurred among persons despite receipt of two doses of MMR vaccine and measurement of high avidity antibody[8-13]. Persons with detectable, but low levels of neutralizing antibody despite receipt of two doses of MMR vaccine, are potentially susceptible to infection and disease[14-18]. When measles is introduced into a highly vaccinated population there are fewer cases of measles; however, among the cases that occur, the relative proportion occurring in vaccinated individuals increases[19].

These cases generally occur in an outbreak or in a setting involving intense exposure to an unvaccinated case of measles, and often exhibit modified symptoms.

While antibody levels are expected to decline over time, it is unclear what effect the absence of natural boosting (asymptomatic secondary immune response) by circulating virus may have in the future on the maintenance of overall population immunity, including the ability of vaccinated persons to transmit virus[20, 21]. Subsequent spread of disease has not been documented from cases of measles with a verified secondary immune response[8-13].

We report on an outbreak of five cases of measles in New York City (NYC) in which a fully vaccinated index case transmitted measles infection to four contacts with presumptive evidence of measles immunity.

Methods

Case and contact ascertainment and investigation

The index case was identified through routine surveillance at the NYC Department of Health and Mental Hygiene (DOHMH). Measles cases were identified by mandatory healthcare provider reports and electronic laboratory notification of positive measles IgM and/or RNA results. Provider reports of immunization records and measles IgG titers done before the onset of illness were reviewed for all cases; verbal reports were not accepted as documentation of immunity. Clinical information and lists of exposed contacts were obtained from a review of medical records and through patient interview. The 2009 Council of State and Territorial Epidemiologists case definition was used to classify confirmed cases[22]. A list of contacts was developed based on identifiable individuals at known exposure sites in NYC. Documented immunization records and measles IgG titers of identified contacts were reviewed and immunity to measles was

determined based on ACIP criteria[7]. Contacts were informed about symptoms of measles and were instructed to contact the DOHMH if they developed measles symptoms. Follow-up with non-immune contacts was conducted again at the end of the incubation period to assure that contacts remained asymptomatic. Exposures occurring outside of NYC were not included in this evaluation.

Laboratory testing

Initial serological and virological testing was performed in several commercial and public health department laboratories. Subsequently, all specimens were sent to the MMR Laboratory at the Centers for Disease Control and Prevention (CDC) for confirmation. Only results from the MMR laboratory at CDC are presented.

Serum specimens were tested for measles specific IgM antibodies using an IgM capture enzyme immunoassay (EIA) as previously described[23]. Measles-specific IgG was tested using an in-house indirect EIA assay incorporating the measles nucleoprotein (N) as the antigen[23]. IgM/IgG index ratios were derived by dividing the net absorbance values measured for IgM by IgG[24]. The IgM/IgG ratio was compared among cases as a measure of primary versus secondary immune response to infection. Index ratios >1 suggested a primary immune response to measles, and ratios <1 were consistent with a secondary response[24].

Avidity of measles-specific IgG antibody was tested by modification of a commercial measles IgG EIA (Captia Measles IgG, Trinity Biotech, Jamestown, NY), as previously described[25]. Measles neutralizing antibody titers were measured using a plaque reduction neutralization (PRN) test performed as previously described[26-28]. Serum specimens were run in parallel with the World Health Organization (WHO) Second International Standard Anti-

Measles serum (IS, coded 66/202, supplied by National Institute for Biological Standards and Control, South Mimms, UK). According to the run validation parameters, a titer of 1:8 corresponded to 8 mIU/mL. Seropositivity was defined as PRN concentrations ≥8 mIU/mL and seroprotection ≥120 mIU/mL[28].

Reverse-transcriptase polymerase chain reaction (RT-PCR) and genotyping were performed. RNA was extracted from nasopharyngeal swab specimens using the QIAamp Viral RNA Mini Kit (Qiagen, Gaithersburg, MD). Measles virus RNA was detected by using a real-time RT-PCR assay targeting the measles nucleoprotein gene as previously described[29]. The measles genotypes were determined following RT-PCR and sequencing using the approach recommended by the WHO[30-32].

Results

The index case was a 22-year-old female resident of NYC with a past medical history only significant for mitral valve prolapse. She developed a generalized rash, cough, conjunctivitis, coryza, sore throat, and subjective fever and presented to an emergency room for medical care but was not hospitalized. She had documentation of receipt of MMR vaccination at 3 years and 4 years of age. There was no travel during the incubation period and no known sick contacts. However, the index case worked at a theater frequented by tourists. Eighty-eight exposed contacts aged 20 years to 65 years were identified in NYC during her infectious period, of whom 66 (75%) had documentation of immunity, 10 (11%) were not immune to measles at the time of exposure, and 12 (14%) had unknown immune status.

Subsequently, four additional cases were identified among contacts of the index case (Table 1). Three of the secondary cases (cases #2, #4, and #5) were healthcare workers at a clinic

where the index case received care and were exposed to the index case on her day of rash onset. Secondary case #3 was a co-worker of the index case and was exposed to the index case two days prior to her rash onset. The secondary cases had no epidemiologic links to any other case of measles in NYC. These secondary cases had a generalized rash with onset between days 12 and 16 after exposure to the index case and ranged in age from 20-52 years (median 30 years). Two of the secondary cases had two documented doses of MMR vaccine and two had prior positive measles IgG antibody results (Table 1). Case #2 had a medical history of immunosuppression and presented with rash, fever, cough, coryza, and conjunctivitis (Table 1). All other secondary cases presented with either rash and fever (case #3) or rash, fever, and cough (cases #4 and 5). None were hospitalized and there were no complications (Table 1).

An additional 231 contacts were identified as exposed to the secondary cases in NYC. Among these exposed contacts, 157 (68%) were considered to be immune to measles or received post-exposure prophylaxis, 5 (2%) were not immune, and 69 (30%) had unknown immune status. No tertiary cases were identified among these contacts.

All cases were laboratory confirmed by a positive measles IgM result, detection of measles RNA by measles RT-PCR, or both (Table 2). Measles IgM was detected in serologic specimens collected 3 or more days after rash onset from four of the five cases. Measles IgG was detected in all serum samples except one sample collected on day 0 from case #2, although the PRN titer from the same serum sample was 1,367 mIU/mL and by day 4 IgG was positive and the PRN titer had increased by over 100-fold. The ratio of IgM to IgG in the day 9 serum from the index case was 9.7, while the other four cases had ratios <1.0 (Table 2). Measles RT-PCR was positive from nasopharyngeal specimens from four of the five cases, two of which were sequenced and identified as genotype D4 (Table 2).

The initial serum samples collected from the index case and case #4 had IgG avidity measured in the intermediate range (end-titer avidity index 63% and 62%, respectively). However, all of the cases had high avidity IgG in follow-up serum samples (Table 2). The PRN titer obtained from the index case was 81mIU/mL in serum collected 2 days after rash and 402 mIU/mL in the follow-up serum collected 7 days later. The four secondary cases had PRN titers of >80,000 mIU/mL in serum collected at ≥3 days after rash onset.

Discussion

An unusual outbreak of measles was investigated in which all of the cases had either two documented doses of MMR vaccine or a positive result recorded for measles IgG antibody in the past. The index case had two documented doses of MMR vaccine before infection and subsequently transmitted disease to four contacts. Although other outbreaks have been reported in which persons with a history of MMR vaccination were confirmed with measles, this is the first report in which a person with measles infection and presumptive evidence of prior immunity based on vaccination history of two doses of MMR subsequently transmitted disease to other individuals[8-13].

The laboratory results of intermediate or high avidity IgG antibody indicate that the index case and all of the secondary cases had past immunologic experience with measles through vaccination or natural measles infection. However, the index's relatively high IgM to IgG ratio was typical of a primary response, while those of the four secondary cases were consistent with a secondary immune response[14, 24]. Although the detection of IgM among measles cases had long been presumed to be a characteristic of the first exposure to measles antigen (i.e. primary immune response), it has since been recognized that IgM can be elicited by persons with either a

symptomatic or asymptomatic secondary immune response, albeit at lower IgM to IgG ratios[14, 24]. Despite high avidity IgG, the index case did not develop the typical high neutralizing antibody titers that have been observed among previously immunized cases[12, 13]. Previous studies noted that extremely high PRN titers in acute phase serum from vaccinated persons with suspected measles infection might serve as a biomarker for cases with a secondary immune response[12, 13]. The four secondary cases all had an early and robust antibody response within a few days after rash onset, with PRN titers 6 to 60 times higher than those observed after primary infection with natural disease or following measles vaccination[12, 13]. Despite more than 200 exposures identified through investigations following notification of the four secondary cases, no additional cases were detected. This is in agreement with other published investigations describing a lack of transmission by documented cases of secondary vaccine failure[8-13]. In each of the secondary cases, neutralizing antibody may have waned sufficiently to allow symptomatic infection, but the anamnestic response upon re-exposure to measles generated a rapid and robust memory response which likely reduced their infectious period. In contrast, the index case's lower neutralizing antibody titer post-infection provides a biologically plausible explanation for her ability to transmit virus.

Previous outbreaks in which symptomatic cases of measles that were later confirmed to have a secondary immune response generally involved measles cases with modified clinical presentations that could easily have been misdiagnosed in the absence of another confirmed case of measles[12, 13]. However, based on the clinical information available, the index and three of the four secondary cases had typical clinical presentations of a generalized rash with duration of 3 or more days with fever, and either cough, conjunctivitis or coryza.

An understanding of the duration of measles immunity is important for ensuring continued success with global measles elimination. Demonstration of waning immunity requires measurement of neutralizing antibody titers before re-vaccination or infection and at time points subsequent to the antigenic stimulation. Detection of IgG is a proxy for immunity, not an absolute correlate of protection from disease. Similarly, the inability to detect measles-specific IgG should not be construed as a lack of immunity in persons who have been previously vaccinated, since cellular immunity and antibody functionality play important roles in protection[17, 33-36]. Neutralizing antibody titers have the closest correlation with immunity to measles, but assays that measure measles neutralizing antibody are not widely available, and tests of cellular immunity are challenging to perform[35, 37]_ENREF_6.

With the achievement of measles elimination, boosting of immunity from exposure to wild type measles virus is uncommon[20]. It is unknown if boosting of immunity among vaccinated individuals by exposure to circulating virus had previously played an important role in maintaining protective levels of antibody, raising questions about the duration of population immunity to measles. In one report of school children in a post-elimination environment, measles neutralizing antibodies persisted for ten years after receipt of a second dose of MMR. Although no seronegative results were detected after ten years, titers did decline over time, with 4.7% (18/382) of the children considered potentially susceptible to infection, given PRN titers in the range of 8-120 mIU/ml; however 72% of those with low titers after ten years had been in the lowest quartile of titers prior to the second MMR dose[17].

There are limitations to this evaluation. Although provider documentation of MMR vaccination was obtained, it is not possible to know about the quality of the vaccine received. Inappropriate storage conditions could alter the effectiveness of vaccine. It is possible that the

cases never responded adequately or only achieved minimal titers following vaccination; however, the laboratory results of high avidity IgG antibody demonstrate that all the cases had responded previously to measles virus and are not primary vaccine failures.

As we move forward on global efforts to eliminate measles, it remains critical that we maintain high population immunity and vigilance for disease. International importations of measles continue to occur in the U.S[6]. The current two-dose MMR vaccination strategy has successfully maintained measles elimination in the U.S. for nearly 20 years, despite continued importations. Now that the U.S. has been free of endemic measles for more than a decade and natural boosting of infection is uncommon, it will be important to better understand the duration of immunity[20, 38, 39]. However, this outbreak probably represents a series of rare events and waning immunity among previously vaccinated persons is unlikely to threaten the ability to sustain measles elimination.

Surveillance also plays a vital role in monitoring the status and duration of population immunity by identifying instances of disease in individuals with prior immunity and conducting investigations of their exposed contacts. Though three of the four secondary cases described in this report had typical clinical presentations, it is important to note that previous outbreaks in which measles cases with a secondary immune response were identified generally involved cases with modified clinical presentations that could easily have been misdiagnosed in the absence of a thorough investigation[12, 13]. A single episode of transmission from an individual with prior evidence of immunity does not justify a change in current measles control and elimination strategies; however, this case clearly underscores the need to maintain sensitive surveillance activities.

Funding

No separate funding was provided for this evaluation outside of funding for routine surveillance and laboratory work.

Acknowledgments

We thank Mekete Asfaw, Vanessa Collado, Antonine Jean, Mohammed Mannan, Francis Megafu, Grace Reyes, and Gamal Sihly, of the NYC Department of Health and Mental Hygiene, David Blythe of the Maryland Department of Health and Mental Hygiene, and Laurie Smalley and India Harris of the Westchester County Department of Health for conducting case and contact investigations, and Laura Walls, Nobia Williams, Rebecca McNall, Elena Lopareva, and Luis Lowe from the Centers for Disease Control and Prevention for laboratory support.

Co-authors have no financial, commercial or other association that might pose a conflict of interest.

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Table 1. Medical history, immunity history and clinical presentation for cases in a measles outbreak in NYC , 2011

		Prior evidence of immunity		Medical history and clinical presentation							
Case	**Age (year)**	**MMR (year)**	**Measles IgG + (year)**	**Medical history**	**Rash[c]**	**Rash Duration (days)**	**Fever**	**Cough**	**Conjunctivitis**	**Coryza**	**Other**
1 (index)	22	1991; 1992	--	Mitral valve prolapse	Y	8	Subjective	Y	Y	Y	Sore throat
2	25	1987 (Poland); 1990	--	Ulcerative colitis, immuno-suppressive medication, cerebral palsy	Y	Unknown	102°F	Y	Y	Y	Diarrhea; Koplick spots
3[a]	20	1992 1996	--	None	Y	4	102°F	N	N	N	Sore throat
4	35	--	2006	None	Y	3	101°F	Y	N	N	N
5[b]	52	--	1993	Hypothyroid on Synthroid	Y	5	Subjective	Y	N	N	N

[a] Case was reported to the NYC DOHMH but investigated by the jurisdiction of residence, Baltimore County DOH

[b] Case was reported to the NYC DOHMH but investigated by the jurisdiction of residence, Westchester County DOH

[c] Generalized

Table 2. Laboratory results from serologic and virologic testing of cases in a measles outbreak in NYC, 2011

Case	No. of serum sample: days from rash onset to collection	IgM Result	IgG Result	IgM/IgG index ratio[a]	IgG Avidity (etAI%)[b]	PRN titer (mIU/mL)	RT-PCR	Genotype
1	Serum 1: 2 days Serum 2: 9 days	Positive Positive	Positive Positive	-- 9.7	Intermediate (63%) High (100%)	81 402	Positive	D4
2	Serum 1: 0 days Serum 2: 4 days Serum 3: 11 days	Negative Positive Positive	Negative Positive Positive	-- -- 0.3	Not done High (83%) High (79%)	1,367 150,219 175,563	Positive	D4
3[c]	Serum 1: 3 days Serum 2: 6 days Serum 3: 11 days	Positive Positive Positive	Positive Positive Positive	-- -- 0.2	High (82%) High (70%) High (73%)	87,155 221,291 168,036	Positive	Not done
4	Serum 1: 3 days Serum 2: 10 days	Positive Positive	Positive Positive	-- 0.24	Intermediate (62%) High (70%)	107,712 94,860	Negative	Not done
5[d]	Serum 1: 3 days Serum 2: 7 days	Negative Negative	Positive Positive	-- 0.02	High (92%) High (97%)	94,860 171,632	Positive	Not done

etAI%= end-titer avidity index; PRN= plaque reduction neutralization; RT-PCR= Reverse-transcription polymerase chain reaction

[a] IgM/IgG index ratio calculated on latest serum available for each case (7-11 days); index ratios >1 suggest a primary immune response to measles and ratios <1 suggest a secondary response

[b] Avidity classified as low (etAI ≤ 30%), intermediate (30% < etAI% <70%) and high (etAI%> 70%); intermediate and high avidity suggest past immunologic experience with measles through vaccination or natural measles infection

[c] Case reported to the NYC DOHMH but investigated by the Baltimore County DOH

[d] Case reported to the NYC DOHMH but investigated by jurisdiction of residence, Westchester County DOH